Effect of Oral Vitamin E Supplementation in Children with Cholestasis

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Abstract

Objective : Malabsorption and deficiency of vitamin E are common consequences of chronic cholestasis. The objective of this study was to determine vitamin E status by using plasma vitamin E/total lipid ratio (E/L) in children with cholestasis during supplementation with 20 IU/kg/day and 100 IU/kg/day of oral vitamin E capsule, and 50 IU/kg/day of cold water soluble form (CWS/F) of vitamin E.

Method : Children with cholestasis who were being supplemented with 20 IU/kg/day of oral vitamin E capsule (dl-α-tocopherol) were enrolled into this study. After initial evaluation for vitamin E status and liver function, doses of oral vitamin E supplementation were increased to 100 IU/kg/day for 1 month. Then, supplementation was switched to 50 IU/kg/day of CWS/F vitamin E for 1 month. Vitamin E status was assessed by using plasma E/L after each period of supplementation.

Results : Eleven children with biliary atresia, aged between 2 and 18 months, were studied. Their median weight standard deviation score (SDS) was -1.35 and median height SDS was -1.26. The medians of serum direct bilirubin and total bilirubin were 6.5 and 12.9 mg/dl, respectively. Only 2 and 3 out of 9 children had plasma E/L above normal cut-off levels during supplementation with 20 and 100 IU/kg/day of vitamin E capsule, respectively. Additionally, 4 of 9 children had plasma E/L above normal cut-off level after one month's supplementation with 50 IU/kg/day of CWS/F vitamin E. All the responders had serum bilirubin levels less than 4 mg/dl while the remainder with serum direct bilirubin level more than 4 mg/dl had their plasma E/L below normal cut-off levels in spite of any vitamin E supplementation.

Conclusion : Oral vitamin E supplementation with 20 IU/kg/day and 100 IU/kg/day of vitamin E capsule and with 50 IU/kg/day of CWS/F vitamin E were able to normalize vitamin E

status in a few cholestatic children who had serum direct bilirubin levels less them 4 mg/dl. In cases of serum direct bilirubin more than 4 mg/dl, neither of vitamin E supplementations was able to correct the vitamin E deficiency status.

Key word : Oral Vitamin E Supplementation, Cholestasis

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Biliary atresia has been detected in 1:10,000 live births. The patients present with neonatal cholestasis which requires diagnosis and management as soon as possible. Treatment with Kasai operation is most successful if performed before 8 weeks of age. In some patients, however, hepatic dysfunction persists. The short-term benefit of Kasai operation is decompression and drainage sufficient to forestall the onset of cirrhosis and sustain growth until a successful liver transplantation can be done. With chronic cholestasis and prolonged survival, patients with biliary atresia may have growth failure which is related in part to malabsorption and malnutrition resulting from ineffective digestion and absorption of dietary fat and fat soluble vitamins[1,2].

Vitamin E is one of the most important lipid-soluble antioxidant nutrients. Vitamin E malabsorption and deficiency occur in up to 60 per cent to 70 per cent of children with cholestasis[3], leading to a degenerative neurologic disorder if deficiency persists beyond age 18 to 24 months[4]. Affected children experience progressive areflexia, cerebellar ataxia, ophthalmoplegia and decreased vibratory sensation. Correction of the deficiency before the age of 3 years can reverse or prevent the development of neuromuscular symptoms. In addition, the vitamin E deficiency state may also cause mild hemolytic anemia, adversely affects immune function and potentiate hepatic injury caused by the underlying cholestasis [5]. Unfortunately, treatment with available forms of orally administered vitamin E is hampered by the impaired intestinal absorption of vitamin E due to insufficient concentration of bile acids during cholestasis. Cold water soluble form (CWS/F) of vitamin E is dl-α-tocopheryl acetate dispersed in gelatin and maltodextrin in order to increase absorbability. The objective of this study was to determine and compare vitamin E status in children with cholestasis during supplementation with oral vitamin E capsule and CWS/F vitamin E.

PATIENTS AND METHOD

Patients aged between 1 month and 6 years who had cholestatic jaundice were studied at the Faculty of Medicine, Ramathibodi Hospital from May 1996 to May 1997. Informed consent was obtained from their parents. The authors excluded patients who had severe infection such as ascending cholangitis or sepsis, severe diarrhea and oral feeding intolerance. Initial evaluation included weight standard deviation score (SDS), height SDS, neurological examination, liver biochemical test and vitamin E status which is best assessed by determining plasma vitamin E/total lipid ratio (E/L). The patients were evaluated while being supplemented with oral vitamin E capsule (20 IU/kg/day) and multivitamin dry syrup composed of vitamin E 7.5 IU per teaspoon (3 teaspoons per day). Then, the dosage of vitamin E supplementation was

increased to 100 IU/kg/day of oral vitamin E capsule, followed by 50 IU/kg/day of CWS/F vitamin E (F. Hoffmann - La Roche Ltd.) for 1 month. Vitamin E status was reassessed after each period of supplementation.

Plasma vitamin E level was measured by high performance liquid chromatography (HPLC) and plasma total lipid concentration was determined by the Bligh and Dyer method[6,7].

RESULTS

Eleven children with biliary atresia aged between two and eighteen months were included in this study. Kasai operation was performed in most of the patients at the median age of 2 months. Their median weight SDS was -1.35 and median height SDS was -1.26. The medians of serum direct bilirubin and total bilirubin were 6.5 and 12.9 mg/dl, respectively, as shown in Table 1.

During the course of study, all of the patients received multivitamin dry syrup which was composed of vitamin E 22.5 IU per day. After supplementation with vitamin E capsule 20 IU/kg/day, for at least one month, only 2 children had plasma E/L above normal cut-off level (0.8 mg/g). When the dose of vitamin E capsule supplement was increased to 100 IU/kg/day for 1 month, only 3 children had plasma E/L above normal cut-off level. Subsequently, 9 children had been given CWS/F vitamin E, 50 IU/kg/day, for 1 month, 4 children had plasma E/L above normal cut-off level. The children with normalized vitamin E status had their serum direct bilirubin levels less than 4 mg/dl while those without normalization had their serum diseased bilirubin levels more than 4 mg/dl (Fig. 1).

DISCUSSION

In the present study, the authors report the results of the supplementation with oral vitamin E capsule and CWS/F vitamin E in children with chronic cholestasis. All 11 children in this study received oral 20 IU/Kg/day of vitamin E capsule before the evaluation of vitamin E status. By this treatment, vitamin E deficiency was corrected in only 2 children with serum direct bilirubin less than 4 mg/dl as shown by plasma E/L above normal cut-off level (0.8 mg/g). When the dosage of oral vitamin E capsule was increased up to 100 IU/Kg/day, only 3 children with serum direct bilirubin less than 4 mg/dl normalized their vitamin E status. Therefore, children with chronic cholestasis who had serum direct bili-

Table 1. The clinical characteristics of the patients.

Patient	Gender	Age (months)	Wt SDS	Ht SDS	Serum direct bilirubin (mg/dl)	Serum total bilirubin (mg/dl)	Plasma E/L after vitamin E Supplementation		
							20 IU/kg/day	100 IU/kg/day	CWS/F 50 IU/kg/day
1	F	10	-3.47	-2.97	1.8	3.1	1.41	1.43	1.2
2	M	5	-2.32	-0.52	3.1	6.8	0.92	0.93	1.46
3	M	5	-3.09	-1.05	3.5	6.9	0.14	2.12	0.9
4	F	4	-2.87	-3.50	3.8	7.2	0.08	0.16	1.32
5	M	4	-1.35	-3.03	4.7	7.9	0.22	0.21	0.13
6	F	5	-1.16	-0.53	6.5	13.5	0.19	0.11	0.19
7	F	2	-0.88	-0.62	8.0	12.9	0.39	0.61	0.42
8	F	6	-1.76	-0.50	9.3	17.5	0.16	0.16	nd
9	M	18	-0.77	-3.43	9.5	19.5	0.11	0.14	0.28
10	F	8	-0.53	-1.26	11.0	20.0	0.12	0.27	nd
11	M	18	-0.18	-1.38	11.3	22.8	0.14	0.07	0.09

nd = no data

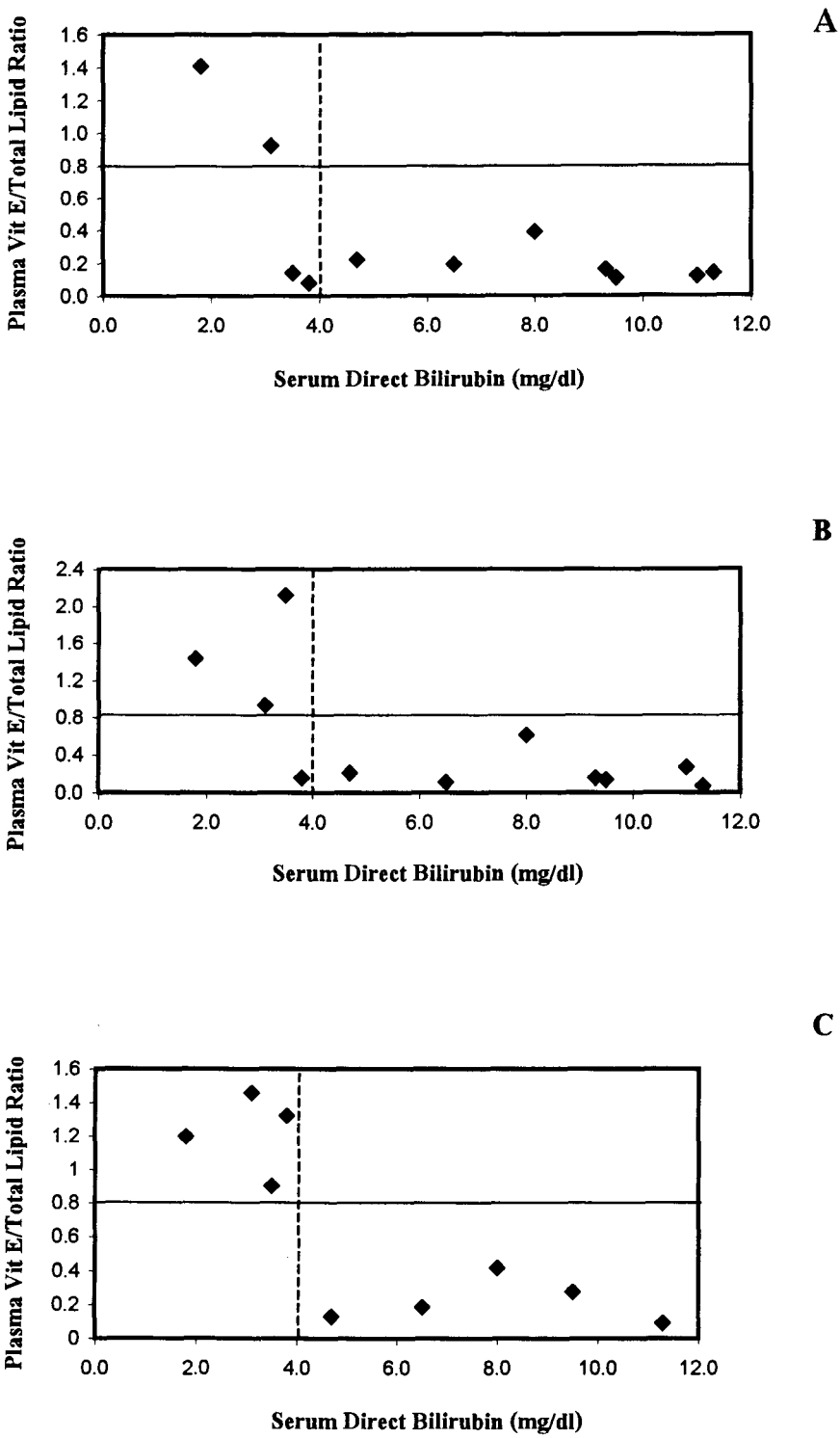

Fig. 1. The relation of serum direct bilirubin levels (mg/dl) and plasma vitamin E/total lipid ratio in children receiving vitamin E supplement of 20 IU/kg/day (A), 100 IU/kg/day (B) in the capsule form, and 50 IU/kg/day (C) in the cold water soluble form.

rubin less than 4 mg/dl were responsive to the supplementation of oral vitamin E capsule.

In order to correct vitamin E deficiency, the patients were supplemented with CWS/F vitamin E, which is dl-α-tocopheryl acetate dispersing finely in a matrix of gelatin and maltodextrin. Four of 9 children responded to 50 IU/Kg/day of CWS/F vitamin E with biochemical normalization of vitamin E status. The remainder whose serum direct bilirubin levels were more than 4 mg/dl were unresponsive to CWS/F vitamin E. Further studies such as increasing the dose of CWS/F vitamin E or using dl-α-tocopherol polyethylene glycol 1,000 succinate (TPGS) are required to reverse vitamin E deficiency in patients with severe chronic cholestasis[8-10].

Although vitamin E deficiency causes neurological disorders[3,11], none of the patients in this study had compatible neurologic abnormalities. According to previous studies in children with prolonged neonatal cholestasis, neurological function was normal in all children younger than 1 year. Between ages 1 and 3 years, neurologic abnormalities were presented in approximately 50 per cent of the vitamin E-deficient children. After the age of 3 years, neurological abnormalities were present in all vitamin E-deficient children[12-16]. Therefore, the children with vitamin E deficiency in the present study were too young to manifest abnormal neurological findings.

The present study has limitations affecting the use of this finding. First, the population of the patients were too small to represent all of the cholestatic patients. Second, the lack of a wash out period between each course of vitamin E supplementation may have had a confounding effect in the interpretation of the results.

SUMMARY

Vitamin E deficiency is common in children with chronic cholestasis. Oral vitamin E supplementation with 20 or 100 IU/kg/day of vitamin E capsule and with 50 IU/kg/day of CWS/F was able to correct vitamin E status in a few cholestatic children who had serum direct bilirubin levels less than 4 mg/dl. In cases of serum direct bilirubin morn than 4 mg/dl, neither of vitamin E supplementation was able to normalize the vitamin E status. Further studies to determine the optimal dose and the effective enteral absorbable forms of vitamin E are required.

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ผลของการให้กินวิตามินอีเสริมในผู้ป่วยเด็กที่มีทางเดินน้ำดีอุดตัน

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ผู้ป่วยที่มีภาวะทางเดินน้ำดีอุดตันเสี่ยงต่อภาวะขาดวิตามินอี เพราะมีความบกพร่องในการดูดซึมวิตามินอี เนื่องจากการขาดน้ำดีซึ่งทำให้เม็ดเลือดแดงแตกง่ายและเกิดความผิดปกติของระบบประสาท ในปัจจุบันการเสริมวิตามินอีโดยการรับประทานในผู้ป่วยกลุ่มนี้ยังเป็นปัญหาในทางปฏิบัติ

วัตถุประสงค์ : เพื่อศึกษาภาวะโภชนาการของวิตามินอีในผู้ป่วยที่มีภาวะทางเดินน้ำดีอุดตัน ขณะที่ได้รับวิตามินอีชนิดแคปซูลรับประทานในขนาด 20 IU/กก/วัน และ 100 IU/กก/วัน และขณะที่ได้รับวิตามินอี ชนิด cold water soluble form (CWS/F) ในขนาด 50 IU /กก/วัน

วิธีการศึกษา : ผู้ป่วยที่มีภาวะทางเดินน้ำดีอุดตัน ขณะที่ได้รับวิตามินอี ชนิดแคปซูลรับประทานในขนาด 20 IU/กก/วัน จะได้รับการเจาะเลือดตรวจการทำงานของตับและวัดระดับวิตามินอีต่อปริมาณไขมันทั้งหมดในพลาสมา (E/L) เพื่อประเมินภาวะโภชนาการของวิตามินอี ก่อนและหลังการเพิ่มขนาดวิตามินอี ชนิดแคปซูลเป็น 100 IU/กก/วัน เป็นเวลา 1 เดือน และเปลี่ยนเป็นวิตามินอี ชนิด CWS/F ในขนาด 50 IU/กก/วัน เป็นเวลา 1 เดือน

ผลการศึกษา : ผู้ป่วยที่มีภาวะทางเดินน้ำดีอุดตันจำนวน 11 ราย อายุ 2–18 เดือน เพศชาย 5 ราย เพศหญิง 6 ราย มีค่า median weight SDS เท่ากับ –1.35 และ median height SDS เท่ากับ –1.26 ได้รับการทำผ่าตัด Kasai operation จำนวน 9 ราย เมื่ออายุเฉลี่ย 2 เดือน มีค่า median ของ serum direct bilirubin และ total bilirubin เท่ากับ 6.5 และ 12.9 มก/ดล ตามลำดับ ขณะที่ได้รับวิตามินอี ชนิดแคปซูลรับประทานในขนาด 20 IU/กก/วัน พบว่า ผู้ป่วย 2 ใน 11 ราย มีค่าระดับ E/L สูงกว่าค่าปกติ (0.8 มก/กรัม) เมื่อเพิ่มขนาดวิตามินอีชนิดแคปซูลเป็น 100 IU/กก/วัน พบว่าผู้ป่วย 3 ใน 11 รายมีค่าระดับ E/L สูงกว่าคนปกติ และเมื่อให้วิตามินอี ชนิด CWS/F ในขนาด 50 IU/กก/วัน ปรากฏว่า 4 ใน 9 ราย มีระดับ E/L สูงกว่าค่าปกติ ผู้ป่วยทุกรายที่มีค่าระดับ E/L สูงกว่าปกติ มีระดับ serum direct bilirubin น้อยกว่า 4 มก/ดล

สรุป : การเสริมวิตามิน อี โดยการรับประทานในรูปวิตามินอีชนิดแคปซูล ในขนาด 20 IU /กก/วัน และ 100 IU/กก/วัน และชนิด CWS/F ในขนาด 50 IU/กก/วัน สามารถป้องกันภาวะขาดวิตามินอี ในผู้ป่วยที่มีภาวะทางเดินน้ำดีอุดตันที่มีระดับ serum direct bilirubin น้อยกว่า 4 มก/ดล เท่านั้น แต่หากมีระดับ serum direct bilirubin มากกว่า 4 มก/ดล การเสริมวิตามินอี โดยการรับประทาน ในการศึกษาครั้งนี้ไม่สามารถป้องกันภาวะขาดวิตามินอี

คำสำคัญ : การให้กินวิตามินอีเสริม, ภาวะทางเดินน้ำดีอุดตัน

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